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ORIGINAL ARTICLE

A randomized, investigator-blinded, controlled, split-scalp study of the efficacy and safety of a 1550-nm fractional erbium-glass laser, used in combination with topical 5% minoxidil versus 5% minoxidil alone, for the treatment of androgenetic alopecia

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Abstract

Fractional 1550-nm erbium-glass (Er:Glass) laser therapy is effective in inducing hair regrowth. Combining fractional Er:Glass laser therapy with topical minoxidil may yield therapeutic benefits for patients with androgenetic alopecia (AGA). To compare the efficacy and safety of fractional Er:Glass laser used in combination with topical 5% minoxidil versus 5% minoxidil alone for the treatment of male AGA, 30 men with AGA were randomized to 24 weeks of split-scalp treatment using fractional Er:Glass laser and 5% minoxidil on one side (combined therapy) or 5% minoxidil alone on the other side (monotherapy). The primary outcome was the difference in hair density and diameter, from baseline, between two treatment sides, at week 24. The secondary outcome was a global photographic assessment, evaluated by two dermatologists and the participants. Adverse events were evaluated. Twenty-nine participants completed the 24-week study period. Combination therapy provided significantly superior results for both the primary and secondary outcomes (all $p < 0.05$). No serious adverse events were identified for either treatment. In conclusion, combination therapy, consisting of fractional Er:Glass laser and topical minoxidil, is a promising treatment option for AGA. Laser-induced photothermolysis and the formation of effective routes for transdermal drug delivery are possible mechanisms. clinicaltrials.in.th, identifier TCTR20160912001

Keywords Androgenetic alopecia · Fractional erbium glass laser · Transdermal drug delivery · Minoxidil

Introduction

Androgenetic alopecia (AGA), or pattern hair loss, is the most common cause of hair loss in males and manifests as a gradual conversion of terminal hairs into vellus-like hairs, called miniaturized hairs. The expression of hair miniaturization is evidently related to the actions of dihydrotestosterone, which is converted from testosterone by 5-alpha reductase enzyme. Hair transformation in male AGA is limited to the frontal, temporal, and vertex areas of the scalp, which are considered to be androgen-dependent regions of the scalp [1].

Various medical and non-medical therapeutic modalities are currently available for the treatment of male AGA. Among treatment options available, oral finasteride, a 5-alpha reductase inhibitor and topical minoxidil have been approved by the US Food and Drug Administration (FDA), with these options providing the best level of evidence in terms of efficacy and safety [2]. For patients who have not achieved successful outcomes with medical therapy, hair transplantation remains an optimal option. In the past years, light and laser therapy has also been increasingly investigated to determine its potential role for the treatment of alopecia [3].

The observation of paradoxical hypertrichosis after laser-assisted hair removal originally inspired the interest in laser phototherapy for the treatment of hair loss. Although the exact mechanism of action of laser phototherapy is still uncertain, the therapeutic effects of several low-level and high-energy

This study was approved by the MU-IRB (Mahidol University Institutional Review Board) on April 30, 2015 (protocol number 03-56-33).

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lasers has been investigated, with evidence of their efficacy for the treatment of alopecic conditions, based on the principal theory of photobiostimulation [3–6]. New hair growth has also been observed after wound healing, with wound-induced follicular neogenesis having been experimentally demonstrated recently [7, 8]. It has been postulated that wounding of the skin induces an embryonic phenotype response, which includes cells of follicular origin, with hair follicles subsequently developing under the influence of Wnt proteins [7, 8].

The therapeutic use of fractional lasers was first developed primarily for skin rejuvenation procedures, with the application for the treatment of alopecia having been subsequently developed. Various types of fractional lasers (including the 1550-nm erbium-glass (Er:Glass) fractionated laser, 2940-nm erbium-yttrium aluminum garnet fractionated laser, 10,600-nm carbon dioxide (CO_2) fractionated laser, and 1927-nm thulium fractionated laser) have been shown to have a positive therapeutic effect in improving hair growth for pattern hair loss and alopecia areata in both animal and human studies [9–20]. Both photobiostimulation and wound-induced hair growth, with skin wounding caused by microscopic thermal wounds resulting from fractional photothermolysis, providing a rational for using fractional laser therapy in the treatment of hair loss.

Apart from the direct effects of fractional lasers on hair regrowth, fractional lasers can also enhance the delivery of topical agents, known as laser-assisted drug delivery [21]. Therefore, the combination of fractional laser therapy with topical agents could provide a synergistic effect, further stimulating hair growth. Evidence of such a synergistic effects was reported in clinical trials of combined therapy, using different fractional lasers (Er:Glass, CO_2, and 1927-nm thulium laser) with topical growth factors [12, 17, 20].

Among fractional lasers that have been used for hair regrowth, the non-ablative fractional Er:Glass laser can penetrate the scalp surface more effectively than other lasers, while providing a coagulation effect [22]. The effectiveness of the Er:Glass laser in inducing hair regrowth has been shown in both animal studies and clinical trials on the treatment of pattern hair loss [9–11]. Moreover, the effectiveness of the Er:Glass laser for laser-assisted drug delivery has also been demonstrated, with pretreatment using the fractional Er:Glass laser improving the penetration of topical 5-aminolaevulinic acid in human participants [23].

Considering the evidence accumulated to date, we hypothesized that the combination of fractional Er:Glass laser therapy and a minoxidil solution, the latter being a standard topical treatment for AGA, could yield a therapeutic benefit for patients with AGA who are not satisfied with conventional treatments. As this combination treatment has not been previously evaluated, our aim in this study was to evaluate the efficacy of fractional Er:Glass laser used in combination with topical 5% minoxidil, compared to 5% minoxidil alone, for the treatment of male AGA. We also evaluated the side effects of these two treatments.

Methods

Study design

This was an experimental, randomized, evaluator-blinded, split-scalp, prospective controlled clinical trial, with a treatment period of 24 weeks, conducted at Ramathibodi Hospital, Mahidol University, Thailand. Follow-up visits were scheduled every 2 weeks. The study was approved by the Mahidol University Institutional Review Board for Ethics in Human Research on 30 April 2015 (protocol number 03-56-33, clinicaltrials.in.th identifier: TCTR20160912001).

Sample size

The sample size was estimated based on data from a previous study of fractional Er:Glass laser therapy in men with AGA [9]. Based on an assumed mean difference in the change of hair density at week 24, from baseline, between the combination therapy (Er:Glass and minoxidil) and monotherapy (minoxidil) of 20 hairs/cm^2, a minimum sample size of 18 participants was required to achieve a power of 80%, with a level of significance of 5%.

Participants

Prospective patients were men with AGA, selected based on the following inclusion and exclusion criteria. The inclusion criteria were a diagnosis of AGA class III–VI, according to the Norwood–Hamilton scale; age > 18 years; and ability to follow the study protocol. The exclusion criteria were the use of oral finasteride or dutasteride within 18 months prior to the start of the trial; use of topical or systemic drugs affecting hair growth within 12 months; scalp light or laser treatment within 6 months; history of hair transplant; and systemic or scalp diseases that may affect hair growth. The date of first enrollment was 4 May 2015. Written informed consent was obtained from all participants.

Treatment protocol

Each side of the scalp (left or right) was randomly selected for the combination and monotherapy for each participant, using a computer-generated randomization table. The fractional Er:Glass laser (Finescan, TNC Meditron, Bangkok, Thailand) and a 5% minoxidil solution were used for all treatments. Both the combination therapy (fractional Er:Glass laser with the 5% minoxidil solution) and monotherapy (5%

minoxidil solution) were continued for 24 weeks. The parameters of the laser therapy were as follows; energy of 6 mJ; density of 300 spot/cm^2; 7 mm probe diameter; and 10% overlapping treatment area. The therapy was applied to one half of the scalp (combination therapy side) at 2-week intervals for a total 12 sessions. One milliliter of topical 5% minoxidil solution was applied to both the combination and monotherapy sides, twice daily. Drug accountability was performed at 6, 12, 18, and 24 weeks. Participants were instructed to maintain the same hairstyle throughout the 24-week study period.

Outcome evaluation

Demographic details for all participants were recorded. Treatment efficacy and safety were assessed at each follow-up visit. The primary outcome was the difference in the change in hair density and diameter from baseline to week 24, measured using trichoscopic photography (Folliscope®; LeadM Corporation, Seoul, Korea), in a target area of 1 cm^2 for both the combination and monotherapy sides. Trichoscopic photographs were obtained at baseline (prior to treatment) and at weeks 4, 8, 12, 16, 20, and 24 over the period of treatment. For repeated and accurate measurements, the target area on each side of the scalp was identified as the intersection point between a horizontal line joining the tip of the tragus and a vertical line extending from the lateral margin of the lateral canthus on the same side. The location of point of intersection of the target area was confirmed by the distance from fixed anatomical locations (namely, the tip of the nose, the right tragus, and the left tragus).

The secondary outcome was a global photographic assessment performed by two dermatologists, who were blinded to the study protocol, and by participants. Photographs of both treatment sides were taken using a Nikon D5100 single-lens reflex digital camera (Nikon Corporation, Tokyo, Japan). Photographs obtained of each side of the scalp at baseline and at the end of the 24-week treatment period were evaluated using a 7-point global assessment scale, as follows: − 3, significant deterioration; − 2, moderate deterioration; − 1, slight deterioration; 0, no change; + 1, slight improvement; 2, moderate improvement; and 3, significant improvement.

Regarding the assessment of safety, follow-up physical examinations were performed and adverse events related to the treatment, such as erythema, irritation, pruritus, erosion, and broken hairs, were monitored throughout the study.

Statistical analysis

Demographic data were analyzed using descriptive statistics. The change in hair density and diameter at 24 weeks, from baseline, was evaluated for each treatment side using a paired *t* test. The significance of the difference in change in hair growth and diameter, from baseline, between the two treatment sides was evaluated using a linear mixed model analysis of variance, with Bonferroni post hoc analysis. Differences in the 7-point rating scale scores between the two sides were evaluated using a chi-squared test. Cohen's kappa was used to evaluate the agreement in score between the two independent observers. Intention-to-treat analysis was performed to evaluate the effects of patient demographics and treatment efficacy, with a per-protocol analysis performed for the assessment of safety. All statistical analyses were performed using SPSS® v. 18.0 (SPSS Inc., Chicago, IL, USA), with a p value < 0.05 was considered statistically significant.

Results

Thirty participants fulfilled the inclusion/exclusion criteria and were enrolled into this study. Of these, 29 completed the 24-week treatment schedule, with one participant dropping out due to the inconvenience of maintaining the required follow-up schedule. The mean age of participants was 35.4 ± 10.3 years, with a mean duration of AGA of 7.3 ± 3.6 years. Baseline characteristics of the study group are summarized in Table 1.

Primary outcome

At week 24, there was a significant improvement in hair density and diameter, from baseline, for both the combination and monotherapy. For the combination therapy, hair density increased from 96.58 ± 16.52, at baseline, to 147.12 ± 18.19

Table 1 Demographics and baseline characteristics of participants

Variable		
Age (years)		
Mean (SD)	35.4 (10.3)	
Duration of AGA (years)		
Mean (SD)	7.3 (3.6)	
	$n = 30$	
Norwood–Hamilton type, *n* (%)		
III	5 (16.7)	
IV	12 (40)	
V	9 (30)	
VI	4 (13.3)	
	Combined	Monotherapy
Hair density (hair/cm^2)		
Mean (SD)	96.6 (16.5)	97.3 (15.9)
Hair diameter (μm)		
Mean (SD)	50.9 (13.6)	51.2 (14.5)

AGA androgenetic alopecia

hairs/cm^2, at 24 weeks ($p = 0.001$), with the hair diameter increasing from 50.93 ± 13.59 to 67.28 ± 15.63 μm, respectively ($p = 0.001$). By comparison, for the monotherapy, hair density increased from 97.25 ± 15.91, at baseline, to 133.77 ± 19.42 hairs/cm^2, at 24 weeks ($p = 0.001$), with the hair diameter increasing from 51.16 ± 14.53 to 65.32 ± 16.42 μm, respectively ($p = 0.002$).

The mean difference of the change in hair density, from baseline, was significantly higher for the combination than monotherapy at treatment weeks 16 ($p = 0.042$), 20 ($p = 0.001$), and 24 ($p = 0.004$), as shown in Fig. 1. For the hair diameter, the mean difference of the change, from baseline, was significantly higher for the combination than monotherapy at treatment week 20 ($p = 0.032$) and 24 ($p = 0.034$), as shown in Fig. 2.

Secondary outcome

There was substantial agreement in the global photographic assessment scores between the two dermatologists (Cohen's kappa = 0.65). This assessment revealed a significant superiority of combination therapy, over monotherapy, in promoting hair growth at week 24 ($p = 0.04$; Fig. 3). Similarly, participants reported superior hair growth on the side treated using the combination therapy, compared to the monotherapy, at week 24 ($p = 0.03$; Fig. 4). Sample global photographs taken at baseline and week 24 are provided in Fig. 5.

Safety

No serious adverse events were reported for either treatment. Adverse events that developed with the combination therapy included tolerable pain and sensation warmth, with these symptoms occurring during the laser treatment period in nine patients, with symptoms resolving spontaneously within a few hours. Other adverse outcomes of the combination therapy included erythema (six patients), itchiness (four patients) and scaling (two patients). Adverse events for the monotherapy included temporary itchiness (five patients) and scaling (three patients). All adverse events were rated as being mild in terms of severity, and resolved spontaneously.

Discussion

The application of fractional lasers for the treatment of AGA has gained wide attention recently, due the efficacy of laser therapy in stimulating hair growth via the stimulation of cytokines by wound healing. Fractional lasers also create an array of microscopic channels across the skin surface that can enhance penetration of topical medication. The findings of our study support the hypothesis that combination therapy, consisting of fractional laser treatment and topical agents (5% minoxidil in our study), can improve the clinical outcomes of hair regrowth. In our study, combination therapy was superior to monotherapy (5% minoxidil alone) in significantly increasing hair density and diameter, as well as global photographic assessment, performed by two dermatologists and participants.

The efficacy of non-ablative fractional Er:Glass laser for the treatment of AGA was first reported by Kim et al. in 2011. They conducted a pilot study of 20 men who received treatment every 2 weeks, for a total of five treatments, with clinical improvement in hair density and growth rate reported, without any serious adverse events [9]. In the same year, Lee et al. conducted a clinical trial of 27 women with female pattern hair loss who received treatment every 2 weeks, for a total of ten treatments. Hair density and diameter revealed a marked improvement after 20 weeks, with adverse events limited to mild puritus and a burning sensation which resolved within 2 h after treatment [10]. Recently, a clinical trial of 23 male patients with AGA, who received treatment every 2 weeks, for a total of 12 treatments, revealed significant increases in hair density and diameter beginning at 16 weeks after treatment initiation [11].

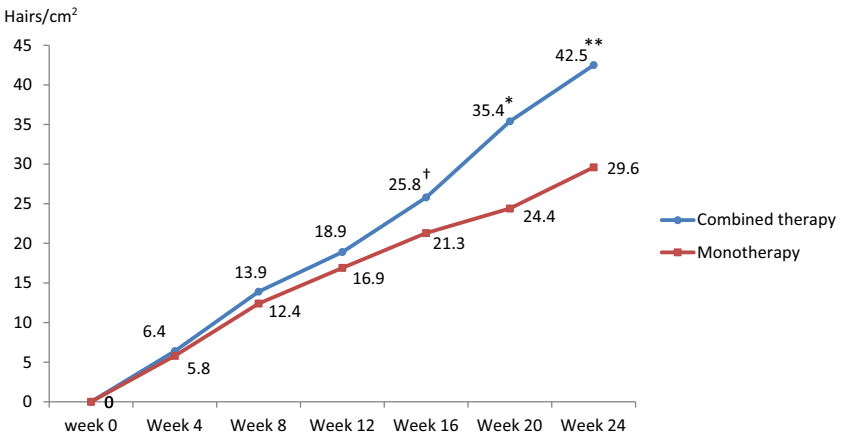

Fig. 1 Differences in hair density in both treatment sides at weeks 4, 8, 12, 16, 20, and 24; †$p = 0.04$, *$p = 0.001$, **$p = 0.004$

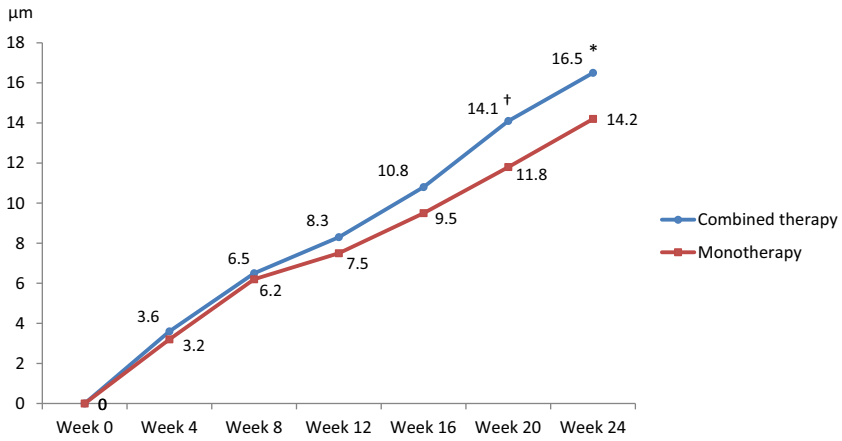

Fig. 2 Differences in hair diameter in both treatment sides at weeks 4, 8, 12, 16, 20, and 24; †$p = 0.03$, *$p = 0.03$

Although the effectiveness of fractional Er:Glass laser to promote hair growth have previously been investigated, the exact mechanisms underlying this therapeutic effect are not well established. Trauma-stimulated wound healing is hypothesized to play a major role in stimulation of hair growth. Stem cells derived from the interfollicular epidermis after wounding were found to regenerate new hair follicles.[7] The laser creates multiple small columns of thermal injury, forming microthermal zones surrounded by normal skin. Cytokine-driven re-epithelialization promotes the healing process [24, 25], resulting in stem cell migration to the damaged areas and dermal papilla cell stimulation [14, 16, 18]. Various cytokines in wound healing, including the fibroblast growth factor family, epidermal growth factor, insulin like growth factor, hepatocyte growth factor, vascular endothelial growth factor (VEGF), and interleukins, have been reported to be important factors for hair growth [25, 26]. An animal study revealed that fractional Er:Glass laser induces hair growth by increasing the Wnt-to-β-catenin signals and by promoting anagen conversion of hair follicle [9]. However, a study of the human scalp revealed that the mechanisms of hair regrowth by laser therapy may not be limited to these pathways [11].

In addition to stimulating hair growth, fractional Er:Glass laser may facilitate transdermal delivery of topical minoxidil, leading to improvement in clinical outcomes. Minoxidil is the only topical drug approved by the FDA for the treatment of pattern hair loss in men and women [2]. The medication enters the skin by normal diffusion or through channels created by fractional laser. Then, it is converted into its active metabolite, minoxidil sulfate, by sulphotransferase enzymes located in the human scalp [27]. The possible mechanism of promoting hair growth includes up-regulation of the levels of VEGF and prostaglandin E2, as well as an increase in blood flow to hair follicle [28].

The optimal parameters of fractional Er:Glass laser for the treatment of alopecia are yet to be established. An animal study suggested that low energy delivered at a high density at 2-week intervals induced considerable hair stimulation [9]. In our trial, as in previous trials, we used low-energy and high-density parameters (300–800 spot/cm^2 density and 5–6 mJ pulse energy, respectively) for laser therapy [9–11]. The parameters used are hypothesized to be effective since they produce a depth of penetration between 500 and 800 µm below the skin surface, which is comparable to the depth of anagen follicles [29]. Low-energy parameters also provide a benefit in

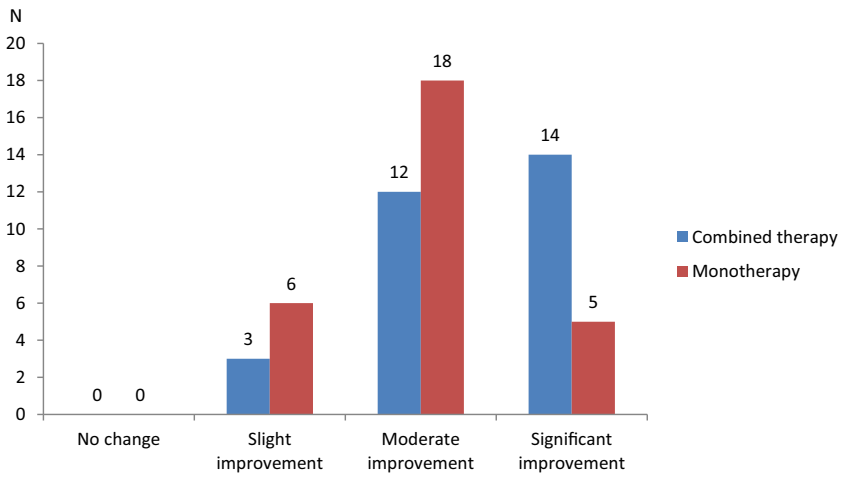

Fig. 3 Global photographic assessment by investigators in both treatment sides ($p = 0.03$)

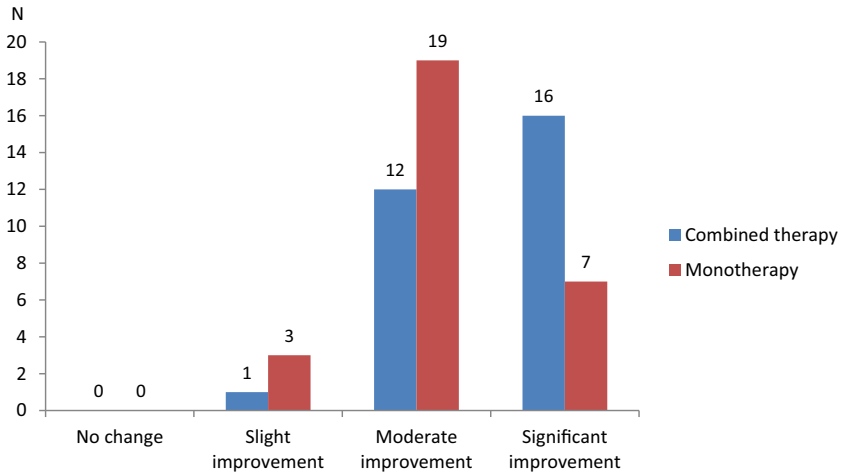

Fig. 4 Global photographic assessment by participants in both treatment sides ($p = 0.04$)

reducing adverse events, such as pain, hair follicle damage, hair shaft breakage, or scalp ulceration.

There was no report of serious adverse events regarding fractional Er:Glass laser for hair loss treatment in either our trial or previous studies [9–12]. Patients in our study felt tolerable pain and a sensation of warmth during laser treatment. Mild adverse effects, such as erythema, itching, and scaling, occurred with both treatments and resolved spontaneously

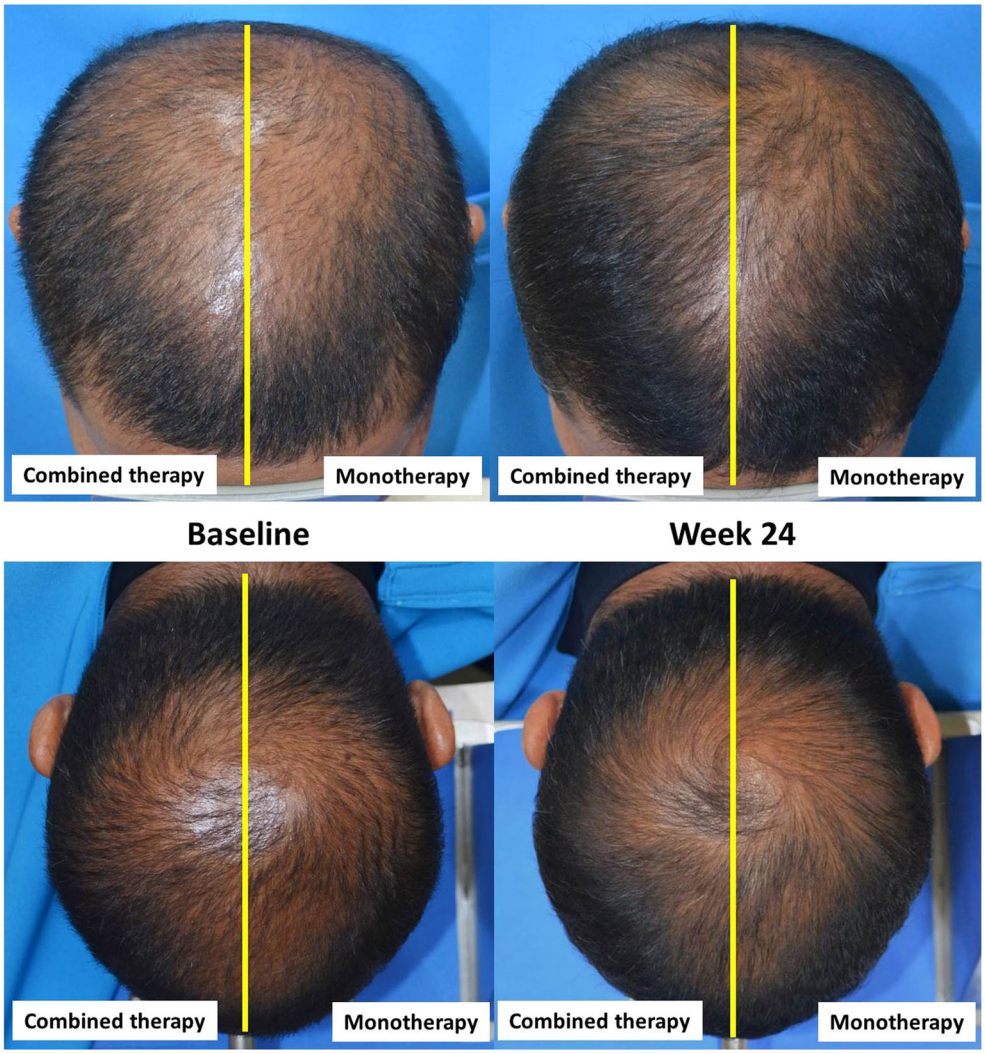

Fig. 5 Baseline and week 24 global photographs of a participant demonstrating the superiority of combined treatment with a 1550-nm fractional erbium glass laser and 5% minoxidil (combined therapy side) over 5% minoxidil alone (monotherapy side)

within a few days. We propose that the combination of fractional Er:Glass laser and topical minoxidil is a safe modality that can be used for adult men and women of all ages.

The limitations of this study include a small number of participants and the use of standardized laser parameters, without assessment of the most appropriate parameters for laser therapy. The 24-week study duration could not evaluate long-term efficacy and safety. Further prospective randomized, double-blind, controlled trials, conducted with a large participant group and a longer study period, are required. Moreover, further research is needed to clarify the mechanisms by which fractional lasers can promote hair growth or increase topical drug absorption, as well as to identify optimal laser for the development of a standard treatment protocol.

In conclusion, our study revealed the superiority of combination therapy, using a fractional Er:Glass laser and 5% minoxidil, over 5% minoxidil alone, for the treatment of male AGA, with no serious adverse effects of treatment identified. Laser-induced photothermolysis and the formation of effective routes for transdermal drug delivery are possible mechanisms explaining the superiority of clinical outcomes for the combination therapy. Fractional Er:Glass laser therapy, either combination with topical agents or monotherapy, can be considered as a promising option for the treatment of AGA.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonization-Good Clinical Practice and local regulatory requirements. The study was reviewed and approved by the appropriate Independent Ethics Committees, and written informed consent was obtained from all subjects prior to study initiation.

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